# The Effects of Space Flight and Microgravity Exposure on Female Astronaut Health and Performance

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*Abstract*—Over the past half century, our understanding of the physiological effects of space exploration and microgravity exposure have improved immensely. Microgravity causes incredible changes to the human body that increase risk of injury upon return to Earth and lunar/planetary egress scenarios. This is due to deconditioning of the cardiovascular and skeletal muscle systems that reduce aerobic capacity and muscular strength. With upcoming exploration class missions, such as NASA's Artemis lunar exploration program which aims to send the first female astronaut to the lunar surface by 2030, as well as a long-term goal of Martian exploration, maintaining astronaut health during extended-duration space flight is critical for achieving mission objectives. However, our understanding of these physiological implications due to microgravity are based primarily on flight studies of male astronauts and 1g bed rest analog study participants, with few investigations focusing specifically on females. Innate physiologic differences in endocrine signaling and reproductive function impact sex-dependent responses to various health conditions, treatments, and environmental factors in nearly every system in the body. Therefore, to assume comparable alterations in females in response to microgravity exposure may be inappropriate and, consequentially, could lead to lasting impacts on female astronaut health and impact mission success. Moreover, differences in sex hormones may also influence the regulation of cardiovascular control during egress activity after space flight-induced deconditioning and blood volume loss (i.e., risk for orthostatic intolerance). Other potential physiological systems and factors related to musculoskeletal health and aerobic capacity that warrant investigation with respect to microgravity include endocrine/reproductive function, vascular control, bone mineral density/microarchitecture, and soft-tissue health. The purpose of this investigation is two-fold: 1) to summarize the data available from space flight and simulated bed rest analog exposures to begin addressing these gaps in knowledge regarding impacts to female astronaut health and 2) to describe differences in demographic health characteristics, injury prevalence, and aerobic capacity and muscular strength in NASA female and male astronauts. Female astronauts make up 50% of the Artemis-specific astronaut corps, and the extent to which microgravity exposure impacts female cardiovascular and musculoskeletal health, and whether these alterations are consistent with their male counterparts, is inconclusive. With the growing inclusion of female astronauts in the NASA space program and the increased duration of missions beyond low Earth orbit, a greater understanding of the sex-specific adaptation to space travel will help determine the development of appropriate countermeasures for minimizing risk and maintaining health of all astronauts.

## 1. INTRODUCTION

Space flight imposes physiological challenges that can cause deconditioning of the cardiovascular and skeletal muscle systems due to microgravity exposure, ultimately reducing aerobic and muscular fitness. This deconditioning can impact the successful completion of mission objectives and increases the risk of injury upon return to Earth and in Lunar/planetary egress scenarios. Additionally, sex-based differences already play an integral role in health on Earth, but presently the basis for our understanding of the physiological changes due to space flight is predominantly based on studies of male astronauts and 1g bed rest analog study participants. Since 2002, the National Aeronautics and Space Administration (NASA) has sponsored several workshops aimed at understanding sex differences with space flight [1]. However, there is a paucity of data and literature to inform space flight-induced health and performance implications for females, which is critical to ensure health and safety and mission success for all astronauts. NASA's Artemis Lunar exploration program, with exploration class missions forthcoming, aims to send the first female astronaut to the Lunar surface by 2030. It will be important to understand the differences in responses between male and female crew so that countermeasures can be optimized to protect the health and performance of all astronauts during these complex and demanding missions.

The current understanding of space flight-induced impacts on physiology and performance comes from studies conducted in a predominantly male astronaut population, resulting from the delayed inclusion of females in NASA's astronaut corps for nearly two decades. Women were initially recruited for the U.S. space program during the early 1960s. In particular, 13 women named the "Mercury 13" successfully completed the same intensive test battery that was used to qualify male astronauts for the Mercury space program. However, funding for the program was canceled and concerns were raised regarding the ability and safety of women to perform as astronauts, preventing women from being included in the Mercury Program [2]. In 1963, the first woman to travel to space was Soviet Cosmonaut Valentina Tereshkova, and the first NASA astronaut class to include women was selected in 1977 [3]. Nearly 20 years after the first women in space, Dr. Sally Ride took part in the historic Challenger Mission STS-7 to low Earth orbit as the first U.S. female mission specialist. NASA has now committed to sending the first female astronaut to the Moon as part of the Artemis Lunar Missions, nearly 60 years after the first male astronaut landed on the lunar surface [4]. While this goal highlights the continued progress and increased diversity within NASA's human space flight program, our understanding of the sex-based space flight physiological impacts remains limited. In order to develop and improve appropriate countermeasures for minimizing risk and maintaining health in all astronauts, a greater understanding of the sex effects on adaptation to space flight is necessary.

This manuscript is comprised of two primary objectives. First, a review of literature was performed in order to summarize the available data from space flight and bed rest analog exposures in order to help address gaps in knowledge regarding impacts to female astronaut health. Specifically, this manuscript focuses on the physiological systems that most impact aerobic capacity and muscular strength. Previously published reviews provide a comprehensive look into other physiological systems that are impacted by space flight and sex [1, 5-7]. Second, a characterization of demographic health characteristics, injury prevalence, and aerobic capacity and muscular strength in NASA female and male astronauts was conducted to inform whether sex differences exist in these measurements.

## 2. REVIEW OF LITERATURE

On Earth, there are innate physiological differences between males and females which can impact susceptibility to and prevalence of various health conditions, treatments, and environmental factors. Careful consideration of sex differences is necessary in the context of space flight, as there is limited research on how sex may moderate physiological responses to micro- and partial gravity. The following review of literature covers physiological systems where sex differences are most apparent (i.e., reproductive and endocrine) and may be implicated in aerobic and muscular health. Where applicable, data from space flight and ground-based analogs are summarized to help describe the physiologic responses in females and elucidate whether potential sex differences in health and performance outcomes exist.

### Endocrine Regulation

The primary signaling pathway responsible for controlling reproductive function in females and males is the

Hypothalamic-Pituitary-Gonadal (HPG) axis. A key function of the HPG axis is to regulate gonadal steroid production, to include the secretion of estrogen and progesterone from the ovaries in females and testosterone from the testes in males. Gonadal steroid hormones impact numerous body systems and can lead to important sex-dependent differences in bone health [8], cardiovascular function [9], and responses to physiological stress [10] and energetic status [11, 12]. These important sex differences were ignored for decades in biomedical and clinical research, as the scientific community considered males an appropriate proxy for all humans [13]. One important distinction between the sexes is the cyclic fluctuations in ovarian hormone concentrations across the female menstrual cycle composed of two distinct phases (follicular and luteal) separated by the release of an egg during ovulation [14]. Considering sex and the hormonal/reproductive distinctions between males and females as important moderating factors in health and performance is imperative to develop a more complete understanding of how space flight impacts human physiology.

The stimulus from exercise can cause the HPG axis to respond in a physiologic or pathologic manner [15] and is exercise duration and intensity dependent. Presently, the NASA in-flight exercise regimen consists of moderate-to-high intensity exercise 6 days/week for 2.5 hr/day, which includes time for set-up, stowage, and personal hygiene. Specifically, the astronaut exercise prescription consists of 30 min/day of aerobic and 60 min/day of resistance exercise, 6 day/week. This level of exercise surpasses the physical activity guidelines outlined by the American College of Sports Medicine [16] and the U.S. Department of Health and Human Services [17], because more exercise is necessary during space flight to maintain astronaut health and performance. As such, understanding the relationship between exercise (or exercise-related energy status) and the HPG hormonal response is an important consideration for highly active astronauts. On Earth, the male HPG axis hormonal response appears to be dependent on duration [18] and intensity of exercise [18]. For instance, total and free testosterone concentrations can be increased by acute bouts of aerobic and resistance exercise [19] in men, whereas testosterone concentrations can decline as a result of excessive training and/or inadequate energy intake [20]. In women, a greater duration of daily exercise has been associated with increased anovulation [21]. A stronger stimulus for HPG dysregulation in exercising women is a chronic energy deficit, which can result from high energy expenditure or low energy intake, and is causally related to reproductive hormone disruption [22], resulting in menstrual cycle disturbances [23]. A greater understanding of external factors, such as exercise and energetic status, that can impact HPG axis regulation is critical for the development of exercise and nutritional countermeasures aimed to maintain health and performance in all astronauts.

*Hormones & Menstrual Characteristics*

Limited research has focused on the impact of space flight and simulated microgravity on female reproduction, which has been studied in rodent models and human bed rest studies. In rodents, one investigation of hindlimb suspension increased estrous cycle length and decreased plasma estradiol concentrations, indicative of hypoestrogenism [24]. Of the limited investigations assessing reproductive function of rodents during space flight, short duration space flight (i.e., 13 days) has been shown to induce cessation of cycling and alter ovarian physiology [25], while longer durations (i.e., 37 days) appeared to have limited impact on estrous cycle activity [26]. However, in studies involving human female participants, bed rest has been shown to have minimal impact on menstrual cyclicity, as reports indicate no effect in menstrual cycle length [27] or the incidence of subclinical menstrual dysfunction (i.e., luteal phase defects) [28]. Notably, study length was not adequate (i.e., 17 days) to confirm impacts on menstrual cyclicity [27]. To our knowledge, no study has reported alterations in menstrual cyclicity or reproductive physiology in response to space flight in female astronauts. Further research is necessary to address the implications of space flight on menstrual cycle and reproductive hormone status. Because estrogen is integral in the regulation of bone health [8] and cardiovascular function [9], understanding whether space flight contributes to hypoestrogenism may have downstream implications for estrogen-mediated physiological processes.

In male animal models and astronauts, microgravity appears to influence the HPG axis endocrine response. Short duration (2 weeks) exposure to microgravity reduced concentrations of testosterone in plasma [29], serum [30], and testicular tissue [29] in male rodents. In male astronauts of comparable microgravity exposure (i.e., 12-13 days), testosterone concentrations reduced by 30% [31]. This is in contrast to longer duration flights which did not affect testosterone concentrations until landing, where a 40-50% reduction of total testosterone, free testosterone, and bioavailable testosterone was reported [31]. Importantly, no investigation has examined sex-dependent differences in reproductive function with space flight or simulated microgravity exposure.

*Hormonal Contraception*

Hormonal contraception use during space flight is a unique consideration for female astronaut health, as combined oral contraception is commonly prescribed to astronauts of reproductive age to suppress the menstrual cycle during missions [3, 32]. For female astronauts, hormonal contraception imparts numerous benefits during space flight such as reduced menses and associated hygiene products, dysmenorrhea (i.e., painful menstruation), and total menstrual flow [3]. Additionally, hormonal contraception used in-flight can serve as a preventive measure to help mitigate the risk of abnormal uterine bleeding and

endometrial disorders during long duration missions [33].

Because pregnancy is a contraindication to space flight and may impact timing of mission selection, female astronauts may choose to suppress their menstrual cycle for extended periods. The potential time frame of menstrual suppression by exogenous hormones, from candidate selection to space flight mission could exceed a decade [32]. However, the effects of chronic hormonal contraception use on other physiology (i.e., bone health) remains unclear. Additionally, the method of administration (e.g., injection, patch, oral, vaginal) may have varied impacts on bone health. For instance, the injectable depot medroxyprogesterone acetate has been shown to reduce bone mass [34] and is no longer prescribed to female astronauts due to a compounded risk of bone loss with space flight. Regarding oral contraceptives, the impact to bone health may be dependent on the formulation, dosage of estrogen, and age of user [35-37], with few prospective investigations to examine the effects of long duration oral contractive use on bone health. To date, no space flight investigation has explicitly examined the impact of hormonal contraception on bone health.

*Bone Health*

On Earth, musculoskeletal sex differences are present across the lifespan [38, 39], as females have lower bone and lean mass compared to males, which is exacerbated later in life during the menopausal transition with the rapid decline in estrogen production. Whether this dimorphic bone health relationship extends to space flight remains to be seen. To our knowledge, only one investigation has examined sex differences in the bone mineral density (BMD) response to space flight. After long duration ISS missions, ranging from 49–215 d, male (n=33) and female (n=9) astronauts showed similar bone density decrements, where total and regional BMD decreased up to 1.5% per month regardless of sex and exercise modality [40]. Though male astronauts had greater BMD compared to female astronauts through the study, consistent with 1g literature, a larger sample size for the female cohort may be necessary to detect sex differences, as sample sizes of 10–20 astronauts with > 2 months of space flight may be required to detect sex differences for space-related changes in BMD [41]. The rate of bone loss (≈1%/month at various sites) could have lasting impacts in all astronauts, and such decline in otherwise healthy female astronauts could put them at risk for early onset osteoporosis and bone-related complications as they approach menopause.

To date, no investigations have examined the impact of space flight on bone structural qualities in female astronauts. Research in male astronauts indicated significant reductions in tibial cortical and trabecular densities (1.5–2%), cortical thickness (4%), and cortical porosity (15%) after 4–6 months on ISS [42]. Importantly, some bone microarchitecture decrements (i.e., tibial cortical porosity and trabecular bone) did not recover after 1 year of reambulation on Earth [42]. A similar finding from a recent investigation indicated that mission duration predicted loss and recovery of bone structural qualities, with longer duration missions resulting in in greater loss and, in some instances, incomplete recovery [43]. Although female astronauts were included in this recent investigation (n=3 of 17 astronauts), researchers did not determine sex differences, likely due to a small female sample size. While bed rest appears to result in sustained decrements to weight-bearing tibia trabecular bone in females [44], further research is necessary to confirm whether space flight results in comparable long-term effects on BMD and bone microarchitecture in female astronauts.

*Tendon & Ligament Health*

Muscle atrophy associated with deconditioning due to space flight may have implications on tendon health, as there have been previous reports of muscle/ligament strain after heavy workload during Apollo Lunar surface operations [45]. Because females are at an increased risk for ligament injury, particularly of the anterior cruciate ligament (ACL), this aspect of space flight deconditioning may be particularly relevant to female astronauts, in which an injury could impact successful completion of EVA objectives or vehicle egress during nominal or emergency landing scenarios. On Earth, females have a 1.7x increased risk [46, 47] for ACL injury compared to males due to a combination of extrinsic and intrinsic factors. Physiologically, evidence from systematic reviews suggest that the cyclic hormonal fluctuations throughout the menstrual cycle may impact ACL tendon health and ACL injury [48, 49], particularly prior to ovulation. Whether oral contraceptive use influences ACL injury remains inconclusive [50, 51]. However, it is important to note that studies assessing menstrual cycle and oral contraceptive effects on ACL injuries are of low quality [52], and whether females are at increased risk for other tendon and ligament injuries warrants further investigation. At present, it is unclear whether exposure to microgravity (1/6g) for lunar EVAs with varied terrain or return to Earth (1g) may lead to increased tendon injury risk in male and female astronauts.

*Body Mass & Energy Requirements*

Generally, females have less body mass, lean muscle, and lower resting metabolic expenditures compared to the average male [53, 54]. During space flight, these characteristics are beneficial, as female astronauts require fewer resources and less energy intake and have less exercise heat production compared to larger male counterparts. However, inadequate energy intake previously reported in male astronauts could have important implications for weight loss, physiological adaptations, EVA performance, and emergency egress in female astronauts.

In early missions, male astronauts experienced 5–10% reductions in body mass [55], largely attributed to inadequate caloric intake with more recent reports indicating

lower decrease in body mass (2–5% decrease) [56]. Insufficient energy intake can manifest in reproductive consequences, as indicated by the male astronauts on Space Shuttle mission STS-55 who consumed only 60–85% of energy requirements [57] and experienced a 46% reduction in circulating testosterone [58]. Importantly, a comparable 5–10% reduction in body mass in female astronauts could induce a cascade of physiological adaptations, including reproduction dysfunction and impaired bone health (i.e., Female Athlete Triad [11]), to conserve energy. Inadequate energy intake, compounded with the known microgravity and radiation-induced decrements to bone density and quality, could further exacerbate bone loss and increase injury risk. Maintaining adequate energy intake and body mass during long duration missions, where food resupply and menu fatigue could be problematic, is essential for the health of all astronauts.

Body mass differences between male and female astronauts may have additional implications for EVA-related task performance, particularly in partial gravity scenarios. A protective pressurized suit is required to perform spacewalks in microgravity and partial gravity environments. Importantly, space suits have not been designed to specific body sizes or individual capabilities, meaning that all astronauts wear and carry comparable suits. For ISS EVAs, the current suit weighs approximately 319 lbs on Earth and is pressurized at 4.3psi differential [59], which can impart significant strength and metabolic burden on smaller astronauts even in a microgravity environment, especially as they work against a pressurized suit. This could increase susceptibility to fatigue, time to completion for EVA-related tasks, and injury risk for smaller female astronauts [5]. For upcoming Lunar exploration, commercially developed space suits will be designed to accommodate a variety of body sizes, but are still estimated to exceed 400 lbs [60]. Importantly, these suits will be used for surface operations in a partial gravity (1/6 g) environment, translating to astronauts wearing/carrying approximately 66 lbs of additional weight during Lunar EVAs. As 50% of the Artemis astronaut corps are female, the ability to use a better-fitting suit is critical for the successful completion of EVA objectives and reduced suited injury risk. Additionally, some crew lose 10–20% aerobic capacity during flight. This reduced fitness in addition to the added weight of suits will increase crew's level of effort to complete long duration EVAs on the Lunar surface and may increase risk of exhaustion and or injury.

## Menstrual Cycle Impact on Performance Variables

Currently, there is debate as to whether endogenous hormone fluctuations in menstrual cycle phases can impact aerobic and strength performance outcomes. Recent systematic reviews and meta-analyses indicate both aerobic and strength performance are minimally impacted by menstrual cycle phase [61, 62] with trivial reductions during the early follicular phase (effect size=0.06) [61]. Similarly, oral contraceptive use appears to have limited impact on performance outcomes, compared to eumenorrheic women [63]. However, the low quality of evidence of the studies included in these systematic reviews [61, 63] and the interactive effect of space flight necessitates continued research to conclusively determine whether menstrual cycle status influences performance. Furthermore, whether menstrual cycle phases influence the exercise adaptive response from aerobic and strength exercise and therefore the ability to maintain performance during space flight is unknown. More research investigating the hormonal influence on exercise outcomes may provide an opportunity to develop targeted countermeasures to maximize female astronaut health and performance during space flight.

## Sex Differences in Aerobic Capacity

Aerobic deconditioning is a known physiologic outcome of space flight [64-66]; however, few studies have directly compared the deconditioning response to microgravity in male and female astronauts. One study in male (n=30) and female (n=7) astronauts investigated the response to submaximal aerobic exercise on ISS missions (mean: 163-day duration), in which heart rate was elevated in both male (8–9%) and female astronauts (11–14%) early postflight (return (R)+5 days), compared to preflight (launch (L)-270 days) values [67]. Additionally, the male astronauts had higher submaximal $VO_2$ values compared to females, as expected. In female astronauts, in-flight aerobic capacity index, a linear extrapolation of HR and $VO_2$ to estimate aerobic capacity, increased linearly throughout the ISS missions and was significantly lower compared to male astronauts [67]. However, the small sample size of females included in the study warrant caution when interpreting the results, as more research is needed to confirm these findings.

Few studies have investigated bed rest-induced changes to aerobic capacity in females. A single investigation demonstrated that submaximal $VO_2$ decreased 11.9% during exercise with a concurrent increase of 6.2% in submaximal heart rate after 17-day bed rest compared to control condition [27] in female participants. A concurrent reduction in mean plasma volume (12.6%) was also reported after bed rest [27]. With longer duration bed rest (i.e., 60 days), $VO_2peak$ has been reported to decrease by 26% in female participants [68]. In an investigation of female twins, 30-day bed rest significantly reduced $VO_2peak$ (−16%) and sprint speed (−24%); however, these responses were comparable to a previous intervention in males [69]. Interestingly, recovery of maximal aerobic capacity after bed rest appears to be hampered in females, as females failed to recover the 13% loss even after 8–9 weeks of recovery [70].

## Sex differences in Muscle Strength and Endurance

Long duration space flight leads to muscle atrophy and strength decrements [71, 72], particularly in the weight-bearing muscles of the lower limbs involved in ambulation.

However, few investigations have evaluated sex differences when determining reductions to muscular structure and function or the time course of muscular changes resulting from unloading. In fact, only one investigation has examined strength changes in both male and female astronauts, where females may experience greater mean decrements to lower limb isokinetic strength following space flight [73]; however, statistical analysis for sex differences were not performed and more research is necessary to determine whether sex moderates strength loss in response to space flight.

Bed rest studies of short duration report greater loss in females compared to males. For example, after 7 days of bed rest, knee extensor isometric peak torque (22–28% reduction in females vs 13–16% in males) and isokinetic peak torque are reduced (7–19% reduction in females vs 0–11% in males) [74, 75]. Additionally, total work (8–18% reduction) and average power (11–19% reduction) was significantly impaired in female, but not male, participants following unloading [74, 75]. Similarly, longer duration bed rest (14-day) in females results in greater reduction in isokinetic knee extensor strength compared to males (16.6% reduction in females vs 4.7% in males) after unloading [76]. One plausible mechanism to support the sex-specific strength decrements, despite comparable muscular atrophy in males and females with bed rest [76], is that differing neural input may be driving these adaptations. Indeed, following unloading, electromyography activity reductions of 27–24% have been documented in females, compared to 8% in males [77]. Based on these results, it is suggested that females have greater loss in leg strength and an impaired capacity to stimulate muscular contraction following unloading.

Importantly, neuromuscular impairment in females appears to occur earlier in immobilization and may require a longer recovery period. For instance, within 48 hours following knee joint immobilization, females experience moderate to large decrements in isometric strength (7.5%), with significant reductions at 1 week (10.6%) and 2 weeks (14.2%) [77]. Similar patterns of impairment were reported with isokinetic strength, which was reduced by 5.5% within 48 hours of immobilization and progressed to approximately 10% reduction in strength at 1 week and 2 weeks [77]. Importantly, females appear to have slower recovery from immobilization. Following 3 weeks of wrist immobilization, male participants fully recovered strength within 1 week, while female participants failed to improve and strength remained 30% lower than baseline values [78]. Notably, the time course for strength decrements and recovery associated with space flight has not been evaluated in female astronauts; however, the data from these immobilization studies provide important insight to demonstrate the need for rapid implementation of exercise countermeasures in order to minimize deconditioning.

# 3. METHODS

*Demographic & Injury Characteristics*

Astronaut demographic and injury data were collected as part of the Lifetime Surveillance of Astronaut Health (LSAH) program. Available data were queried from NASA astronauts who participated in Mercury missions through ISS Expedition 66 (n=360), as of August 2022. Diagnosed musculoskeletal injuries and conditions were queried from the LSAH database to include muscle sprain/strains, tendonitis, ACL injuries, and diagnoses of osteopenia and osteoporosis. Injuries were reported as occurring in-flight or postflight (ranging from R+0 days to 2 years postflight).

*Aerobic and Muscular Strength Performance Characteristics*

Pre- and post-mission outcomes from the ISS crewmember standard medical assessments ("MedB") were analyzed to determine whether sex differences exist for aerobic and strength space flight deconditioning. Aerobic and muscular fitness testing occurred at NASA Johnson Space Center in Houston, TX.

Aerobic capacity ($VO_2pk$) and power (W) were assessed via an upright cycle ergometer (Lode, Groningen, Netherlands) in 11 female and 36 male astronauts. Methods and calibration for $VO_2pk$ testing has been previously described [79]. Briefly, crewmembers followed a ramped protocol that included a 3-minute warmup at 50 W, with stepwise increases in resistance (25 W every minute) until volitional fatigue. $VO_2pk$ was measured via a metabolic gas analyzer (Parvo Medics, Salt Lake City, UT, USA) and was defined as the highest recorded value attained using 30-second averaging. Preflight data collection for aerobic capacity and power occurred at L-3/1 month and postflight data collection at R+3 days.

Muscular strength and endurance were assessed via isokinetic testing in 17 female and 70 male astronauts. As outlined in the NASA Medical Volume B 5.3 (isokinetic testing), preflight data collection for muscle strength and endurance occurred at L-3/1 month and postflight data collection at R+5 days. Methods for isokinetic testing has been previously described [73]. Briefly, crewmembers wore athletic clothing and footwear and completed a 5-minute warmup (50 W) on cycle ergometer (Lode, Groningen, Netherlands). Isokinetic testing was performed in a dynamometer (Biodex, Shirley, NY, USA), with calibrations performed prior to each testing session. The dynamometer was adjusted to each crewmember, with position settings recorded at preflight to ensure correct position at the postflight measurement. A handheld goniometer was used to measure the anatomical reference point in a seated position for the knee (90°), and knee strength was assessed over a range of motion from 95° for flexion and 20° for extension. Knee extension and flexion strength were assessed at 60°/s (concentric/concentric) during five maximal efforts. Knee extension endurance was assessed at 180°/s (concentric/concentric) during 21 consecutive maximal repetitions. All data are reported as mean ± standard deviation.

### Statistical Methods

Data was assessed for normality using the Shapiro-Wilk test. For normally distributed variables, independent t-tests were performed to compare preflight demographic data and percent change data between female and male astronauts; for non-normally distributed data, the Mann-Whitney U test was performed. GraphPad Prism 9 (version 9.3.1) was used for analyses. Data were reported as mean ± SD, and the significance level was α=0.05. The data presented in this manuscript represents private medical information; therefore, the data provided by LSAH for this manuscript was de-identified and stratified by sex.

## 4. ANALYSIS OF CREW DATA

### Demographic Characteristics

As of 2022, there have been a total of 360 people selected as NASA astronauts. Of these, a majority have been male (83%), with only 17% of NASA astronauts being female (Table 1). Similarly, female astronauts have performed far fewer space flight missions (12.7% vs 87.3% of male space flight missions). Age at selection was comparable between male and female astronauts, all falling with the range of 25–46 years of age. Likewise, male and female astronauts were of similar age at the time of their first space flight mission, which, on average, occurred 6 years after selection.

**Table 1. NASA Astronaut Demographics Grouped by Sex**

| Demographics | Male | Female |
|---|---|---|
| **Astronauts (n, %)** | 299 (83.1%) | 61 (16.9%) |
| **Astronauts with ≥ 1 space flight (n, %)** | 270 (84.4%) | 50 (15.6%) |
| **Space Flight Missions (n, %)** | 955 (87.3%) | 139 (12.7%) |
| | Mean±SD | Mean±SD |
| **Age at selection (yr)** | 34.4±3.7 | 32.5±3.5 |
| **Age at first mission (yr)** | 40.7±4.6 | 37.8±4.2 |
| **Flight Duration (days)** | 25.7±49.7 | 40.6±68.7 |
| **Cumulative Duration in Space (days)** | 67.6±94.8 | 102.4±127.2 |

### Injury

Preliminary data (as of August 2022) for astronaut musculoskeletal injuries and diagnoses include those determined to be muscle sprains/strains, tendinitis/tendinopathy, fracture, and diagnosis of low bone mineral density. A total of 283 musculoskeletal injuries were reported (either in-flight or postflight) in 151 astronauts (Figure 1). Approximately half of these astronauts (49.7%) had multiple diagnosed injuries, with an average of 1.8 injuries reported per astronaut (range 1–8 injuries). The most diagnosed injuries were classified as muscle strains/sprains (59%).
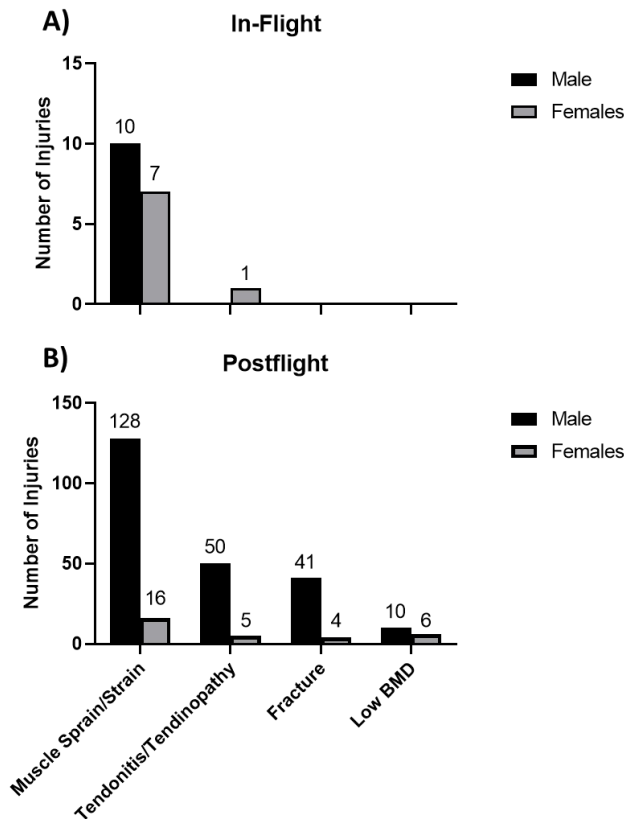
**A)** In-Flight

**B)** Postflight

**Figure 1. In-flight and Postflight Injuries in Female and Male Crewmembers**

Of these specific conditions, a majority of musculoskeletal injuries occur postflight (260/283; 92%), with far fewer occurring in-flight (18/283; 6%) or at landing (5/283; 1%) (Figure 1). During the postflight period, the most common injuries were muscle strains/sprains (55%) and occurred mainly in the back, neck, shoulder, and leg. Tendon-related injuries were the second most prevalent group of injuries postflight (21%), occurring mainly in the shoulder, elbow, wrist, and ankles. Interestingly, only two ACL injuries were reported postflight, both occurring in male astronauts. On average, postflight injuries were diagnosed 352±217 days post-landing. A majority of postflight injuries (49.6%) occurred of within 1 year of landing, with 7.3% occurring within 1 month, 8.1% occurring between 1–3 months, 9.2% occurring between 3–6 months, and 25% occurring between 6–12 months after landing. These data suggest a continued prolonged exercise rehabilitation program may be needed to reduce postflight injuries for all crewmembers.

Fewer total musculoskeletal injuries were reported in female astronauts (39 injuries in 20 participants) compared to males (244 injuries in 131 participants) (Figure 1), though prevalence was slightly higher (1.95 injuries per female, 1.86 injuries per male). Despite in-flight injuries occurring less frequently overall, in-flight injuries made up 20% of injuries reported in female astronauts, compared to 4% in males. Postflight injuries, which made up 94% of male and

80% of female astronaut musculoskeletal injuries, muscle strains/sprains were comparably prominent in all astronauts. However, diagnoses of low BMD appeared higher in female astronauts (15%) compared to male astronauts (4%).

*Sex differences in Aerobic Capacity*

Aerobic capacity in the ISS cohort demonstrated that female crewmembers were significantly younger, weighed less, and had lower relative aerobic fitness compared to their male counterparts at the L-3/1 month preflight timepoint (Table 2).

**Table 2. Preflight Astronaut Aerobic Capacity Demographics**

| | Female (n=11) | Male (n=36) | P-value |
|---|---|---|---|
| Age (yr) | 44.5±6.6 | 48.6±5.6 | 0.041 |
| Body Mass (kg) | 68.8±10.0 | 81.0±8.8 | < 0.001 |
| Flight Duration (days) | 205.0±58.3 | 176.0±40.5 | 0.061 |
| VO$_2$peak (ml/kg/min) | 32.8±5.9 | 37.8±6.0 | 0.021 |
| Peak Watt (W) | 229.0±41.5 | 299.0±52.4 | < 0.001 |
| Peak Heart Rate (beats/min) | 176.0±7.3 | 173.0±10.8 | 0.406 |

Female and male crewmembers had comparable flight durations (Table 2) and demonstrated similar reductions in VO$_2$peak (Figure 2A), as females decreased 11.8%±10.7% and males decreased 8.8%±7.9% from pre to postflight (p=0.318). Notably, females had a greater reduction in maximal external work in compared to the male crewmembers (Figure 2B; −13.3%±-8.9% vs −4.9%±-8.8%; p < 0.01). However, there is notable inter-individual variability in pre-to-postflight changes in both sexes. A larger sample in females, controlling for age and flight duration, are needed to confirm these preliminary findings.
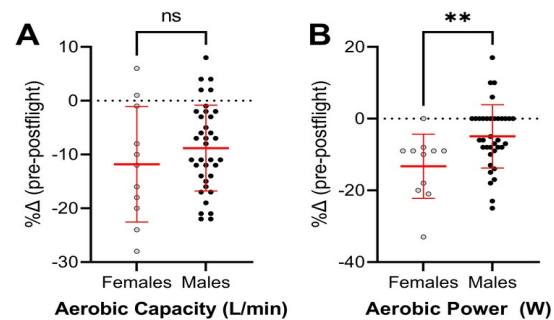


**Figure 2. Sex differences in aerobic capacity and power**

*Sex differences in Muscle Strength and Endurance*

Strength measurements in the ISS cohort demonstrated that female crewmembers had lower absolute muscular strength and endurance compared to their male counterparts at the L-3/1 month preflight timepoint (Table 3). When normalized to body mass, knee extension strength was not different between female and male crewmembers (Table 3).

**Table 3. Preflight Astronaut Strength Demographics**

| | Female (n=17) | Male (n=70) | P-value |
|---|---|---|---|
| Age (yr) | 42.8±3.7 | 48.4±5.1 | < 0.001 |
| Body Mass (kg) | 65.7±6.3 | 82.9±8.4 | < 0.001 |
| Flight Duration (days) | 179.0±50.3 | 173.0±33.3 | 0.478 |
| Knee Extension Strength (Nm; 60/sec) | 150.0±24.6 | 206.0±42.0 | < 0.001 |
| Normalized Knee *Extension* Strength (Nm/kg; 60/sec) | 2.3±0.3 | 2.5±0.5 | 0.199 |
| Knee Extension Endurance (Nm; 180/sec) | 1546±507 | 2374±585 | < 0.001 |
| Normalized Knee Extension Endurance (Nm/kg; 180/sec) | 23.7±6.4 | 28.7±7.0 | 0.019 |

Preliminary findings from ISS data show that isokinetic knee extension strength decreased by 17.2%±13.3% and 9.9%±14.7% in female and male crewmembers, respectively, after space flight, although there was no statistical difference between the sexes (Figure 3A; p=0.063). Similarly, isokinetic knee endurance decreased comparably by 13.6%±14.7% and 12.1%±12.7% in female and male crewmembers, respectively (Figure 3B; p=0.921). A larger sample in females, controlling for age and flight duration, are needed to confirm these preliminary findings.
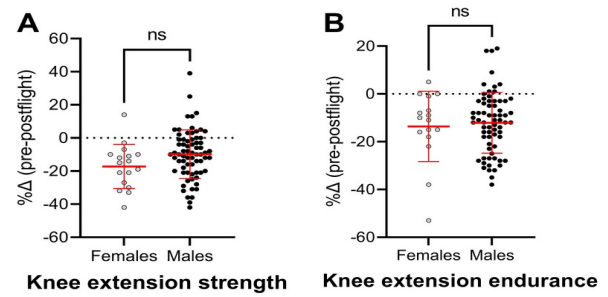


**Figure 3. Sex differences in isokinetic knee extension strength and endurance**

## 5. CONCLUSION

With exploration class missions quickly approaching, a clear understanding of how the physiological effects of space flight differ between male and female astronauts is imperative. Determining whether sex differences exist in aerobic and strength deconditioning could inform targeted countermeasures to help mitigate risks and keep all astronauts safe across a variety of environments and situational demands. Despite the increased attention towards addressing this gap in the space flight literature, more research specifically aimed at understanding how female astronauts physiologically adapt to space flight and how this could vary from their male counterparts is still required.

While NASA has made efforts to increase the diversity within recent astronaut classes, to include an equal distribution of male and female astronauts in the Artemis-specific astronaut corps, our data demonstrate that male astronauts remain the overwhelming majority of all NASA astronauts. Interestingly, despite comparable age and time to first mission, the average flight duration for female astronauts is nearly double that of their male counterparts, resulting in greater cumulative days in space compared to male astronauts. This average difference in duration between the sexes is because the space flight missions of short duration during these early programs (i.e., Mercury, Gemini, and Apollo) included only male astronauts. As both male and female astronauts are a part of longer duration ISS missions and future exploration class missions to the Moon and Mars, understanding how extended microgravity and partial gravity exposure impacts all astronauts is imperative.

Regardless of sex, space flight-induces deconditioning, increases risk of injury, which could impact the ability to complete EVA-associated tasks or compromise an astronaut's ability to safely egress in contingency scenarios. Importantly, far fewer injuries were diagnosed in-flight, with a majority—mainly muscle sprains/strains—occurring postflight. This indicates that few injuries are occurring in the microgravity environments; it remains to be seen whether the partial gravity environments of Lunar or Martian surfaces would impact the prevalence of in-mission injuries. Additionally, our findings demonstrate that fewer musculoskeletal injuries and diagnoses occurred in female astronauts, most likely due to the fact that there have been historically fewer female astronauts. While fewer injuries are reported in females, the proportion of injuries that occurred in-flight was greater than that reported in males. Similarly, the proportion of low BMD diagnoses in female crewmembers postflight was 3x that of male astronauts. Together, these data provide important information regarding the health of all astronauts and may be informative for the continued improvement of preventative exercise countermeasures to help minimize the risk of musculoskeletal injury.

While our data demonstrated an overall greater aerobic capacity in male astronauts preflight, there were comparable reductions in $VO_2$peak between the sexes. This is consistent with what has been reported in the limited space flight and bed rest studies investigating responses in both male and females. However, female astronauts experienced a greater reduction in maximal external work (peak watt). More research is warranted to elucidate the cause of this disparity, which may be due to differences in blood volume, vascular function, oxygen delivery, and skeletal muscle oxidative metabolism. Similarly, reductions in normalized knee extension strength and endurance were comparable, although a larger sample size in the female cohort controlling for age and flight duration, as well as further health and performance evaluations, are needed to confirm these preliminary findings.

While the data reported here help to address the gap in knowledge regarding sex difference aerobic and muscular deconditioning with space flight, important limitations to this dataset must be considered. Injuries reported herein do not fully encompass all injuries diagnosed by crew flight surgeons and only represent a subset of musculoskeletal injuries identified as being relevant to muscular deconditioning. Additionally, aerobic and strength deconditioning data are limited by small sample sizes which may not have been adequately powered to detect differences in aerobic capacity, knee extension strength or endurance. These analyses were not controlled for age or flight duration which could also influence deconditioning outcomes.

Research is limited in the understanding of hormonal response to exercise. Major knowledge gaps include space duration effects on estrogen and testosterone. Additionally, it is currently unknown whether sex-dependent differential responses to space flight deconditioning and estrogen/testosterone hormones are affected by the adaptions to exercise for maintaining bone, tendon/muscle strength, and aerobic capacity. If so, specific sex dependent countermeasures may be needed to address this potential issue. Lastly, recovery of muscle strength following space flight has been reported to be slower in females. Further understanding is needed to improve postflight rehabilitation measures for all astronauts.

In order to protect all crew, adequate data and research are necessary to inform the critical decisions regarding risks and countermeasure development for long-duration exploration missions. This report has outlined several gaps that can be filled with directed investigations to better characterize the physiological adaptions to space flight in female astronauts.

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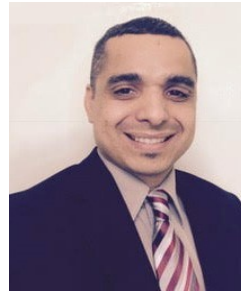


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